PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4-32837A/DFC		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 03/06091	16.12.2003	20.12.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K31/502		
Applicant		
DANA-FARBER CANCER INSTITUTE INC. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the International application

Date of submission of the demand	Date of completion of this report
19.07.2004	03.03.2005
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 03/06091

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-6 as originally filed

Claims, Numbers

1-12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-9 (industrial applicability); 1,2,5-11 (in part)

because:

☒ the said international application, or the said claims Nos. 1-9 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1,2, 5-11 (in part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 11,12
	No:	Claims	10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	10; for 1-9,11,12 see separate sheet
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 1-9** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. No International Preliminary Examination will be carried out in respect of subject-matter which is not covered by the International Search Report (see Rule 66.1(e) PCT), i.e. in respect of 4-pyridylmethyl-phtalazine derivatives not falling within the formula I as specified in claim 3.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. The documents referred to in this International Preliminary Examination Report as **D1**, **D2**,... are those cited in the International Search Report. They have been numbered according to their order of citation therein.

4. The present application relates to a method of treating VHL (**claim 1**), and VHL-related hemangioblastoma (**claim 2**) comprising administering a 4-pyridylmethyl-phtalazine derivative (alternatively in combination with surgery and/or radiation therapy, claim 9). **Claim 10** is directed to a commercial package comprising a 4-pyridylmethyl-phtalazine derivative together with instructions for use in the treatment of VHL and/or VHL-related hemangioblastoma. **Claim 11** is drafted in the second medical use format.

5. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33(2)) for the following reasons.

Both, **D1** and **D2** discloses 4-pyridylmethyl-phtalazine derivatives for the treatment of various disorders, including hemangioblastoma and hemangioma. However, the treatment of VHL-related hemangioblastoma is not mentioned. Therefore, said documents are novelty destroying only for **claim 10**.

The following observation is made with respect to present **claim 10**. Said claim is directed to a commercial package comprising a 4-pyridylmethyl-phtalazine derivative together with instructions for use in the treatment of VHL and/or VHL-related hemangioblastoma. It should be noted that the feature "with instructions for use in the treatment of..." is not regarded as a distinguishing feature over a pharmaceutical composition comprising a 4-pyridylmethyl-phtalazine derivative as active agent. Therefore, said claim does lack novelty not only over **D1** and **D2** but also over any document disclosing the 4-pyridylmethyl-phtalazine derivative in connection with any therapeutic use.

6. Furthermore, the present application does not meet the requirements of the PCT with respect to inventive step (Art. 33(3)).

D3, which is regarded as the closest prior art, discloses the treatment of VHL syndrome and optic nerve head hemangioblastoma by systemic administration with the VEGF inhibitor SU5416. The present application according to claims 1-12 differs from **D3** in that other VEGF inhibitors are used, namely the derivatives disclosed in **D1** and **D2**. Thus, the problem to be solved by the present application is the provision of alternative VEGF inhibitors useful for the treatment of VHL.

The solution proposed in the present application is the use of the VEGF inhibitors disclosed in **D1** and **D2** is obvious. In the light of **D3**, the skilled person would consider obvious to try the VEGF inhibitors disclosed in **D1** and **D2** as potential therapeutic agents in the treatment of VEGF.

7.1. For the assessment of the present **claims 1-9 and 11-12** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known

compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7.2. **Claim 10** meet the criterion set forth in Article 33(4) PCT because its subject-matter is susceptible of industrial application.